Bianca Leuthe

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/050799	25.02.2005	27.02.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K45/06 A61K31/575 A61K31/4015 A61P11/00 A61K9/00

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Kanbier, D Telephone No. +31 70 340-3465

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. partly 1-8, 10-19

because:

☒ the said international application, or the said claims Nos. 14-18 with respect to industrial application relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. partly 1-8, 10-17, 19; see separate sheet

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-13, 19
	No:	Claims	14-18; see separate sheet

2. Citations and explanations

see separate sheet

Re Item III.

1. Claims 14-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. An International Search Report was drawn up for the present set of claims, as far as the subject matter included therein is sufficiently defined and supported by (further) claims and by examples, with due regard to the general idea underlying the application as provided by the description. For subject matter of the present application excluded from the search on this basis, no opinion with regard to novelty and inventive step is included in this preliminary examination. The following is a specification of the reasons for possible exclusion of part of the application's subject matter from search and thus from preliminary examination:

2.1 Present claims 1-8, 10-17 and 19 relate to methods and compositions involving an extremely large number of possible compounds by use of the terms "derivatives". Due thereto, a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to have rendered a meaningful search over the complete scope of the claims impossible.

2.2 Consequently, the search has been carried out for those parts of the claims which appear to be clear (and concise), supported and disclosed, namely those parts relating to the compounds specifically disclosed in a claim or example of the application, with due regard to the contents of the description.

Thus claims 1-8, 10-17 and 19 have been searched in part.
In as far as the above objections could be envisaged to be overcome (e.g. by appropriate amendments), the resulting searched subject matter gives rise to the following objections to patentability under the PCT:

Re Item V.

For the assessment of the present claims 14-18 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:
D1 : US 6 645 466 B1 (KELLER MANFRED ET AL) 11 November 2003
D2 : WO 00/07567 A (JAGO RESEARCH AG) 17 February 2000
D3 : WO 02/083113 A (DEY, L.P; BANERJEE, PARTHA, S) 24 October 2002
D4 : WO 02/47668 A (BOEHRINGER INGELHEIM PHARMA KG) 20 June 2002
D5 : WO 01/76575 A (ARAKIS LTD) 18 October 2001
D4 and D5 were cited by the applicant in the description of the application.
D1, D2 and D3 disclose inhalable triple combinations of betamimetics (e.g. formoterol), anticholinergics (e.g. tropium or glycopyrronium salts) and glucocorticoids (e.g. ciclesonide). These inhalable formulations consist of dry powders in D1-D3, with lactose as a carrier in D1 and D2. They are used to treat airway diseases like asthma.
D4 discloses a combination of ciclesonide with anticholinergics, notably with tropium salts, as an inhalable powder on lactose, for treating asthma, COPD, etc.
D5 discloses combinations of glycopyrrolate with a number of types of further actives, including glucocorticoids. Ciclesonide is not mentioned; neither is lactose as a carrier, although polysaccharides are envisaged.

INVENTIVE STEP

3. In view of D1-D3, the subject-matter of claims 1-19 can not be considered inventive (Article 33(3) PCT) for the following reasons:

3.1 In view of the disclosures of these documents, it is clear that combinations comprising glucocorticoids and anticholinergics (with ciclesonide and glycopyrronium (salts) being mentioned as specific examples of these functional compounds), formulated as inhalable powders on lactose, for treating asthma, COPD and other airway diseases, are known in the prior art.

3.2 In such a situation, the skilled person would, when searching to provide alternative anti-asthma treatments, combine these compounds as mere replacements of

representative compounds in their class, while expecting at least some beneficial effect in the treatment concerned.

3.3 To render the combination inventive, an unexpected effect (e.g. synergy) would have to be convincingly demonstrated.

3.4 Although the present application alleges a synergistic effect of the combination (page 2, paragraph 5), it is not, in fact, demonstrated in the application. Therefore present claims 1, 14 and 19 lack an inventive step.

3.5 Dependent claims 2-13 and 15-18, in as far as not disclosed or directly indicated in the available prior art, represent mere alternatives of known compounds and measures of practice to a skilled person.

4. In view of D4, which is considered to represent the closest state of the art, the subject-matter of claims 1-19 can not be considered inventive (Article 33(3) PCT) for the following reasons :

4.1 The difference between the present claims and D4 lies in the choice of anticholinergic compound in the combinations with ciclesonide as claimed in D4. D4 only refers to tropium salts as anticholinergic compounds.
However, it is generally well known, and besides demonstrated in D1, column 6, lines 18-19, that glycopyrronium (salts) are anticholinergic compounds that can be used without inventive effort to replace tropium salts in the formulations and therapeutical uses of the present application.

4.2 Therefore, the skilled person would, when searching to provide alternative anti-asthma treatments, arrive without inventive effort at the subject matter of the present claims when replacing tropium salts with glycopyrronium (salts).

4.3 To render the combination inventive, an unexpected effect (e.g. synergy) would have to be convincingly demonstrated.

4.4 Although the present application alleges a synergistic effect of the combination (page 2, paragraph 5), it is not, in fact, demonstrated in the application. Therefore present claims 1, 14 and 19 lack an inventive step.

4.5 Dependent claims 2-13 and 15-18, in as far as not disclosed or directly indicated in the available prior art, represent mere alternatives of known compounds and

measures of practice to a skilled person.

D.T. Kanbier